REMARKS

Applicants respectfully request entry and consideration of the present amendment under 37 C.F.R. § 1.116(a) because numerous rejected claims have been canceled, placing the application in condition for allowance or in better form for appeal. In addition, as discussed in more detail below, because the Examiner did not properly consider the Second Declaration submitted with the last reply, Applicants respectfully request that the Examiner withdraw the finality of the present office action, and enter and properly consider the Second Declaration and the arguments presented regarding the Second Declaration in this and in the previous response filed on July 30, 2003.

Claims 1-86 are canceled without prejudice. New claims 123-125 merely split the polypeptides recited in claim 1 into separate claims. Applicants reserve the right to pursue the canceled subject matter in one or more continuing applications. Claims 87-125 are pending and under examination. No new matter has been added.

A notice of appeal is being filed herewith.

The Second Declaration

In the instant Office Action, the Examiner states that the Declaration filed with the response on July 30, 2003 ("the Second Declaration") would not be considered until a signed copy arrives. However, Applicants submitted a Supplemental Reply containing a signed copy of the second Declaration on August 19, 2003, a full 3 months before the present office action was mailed. A copy of this Supplemental Reply, which includes a certificate of facsimile transmission and cover sheet indicating successful transmission of the facsimile, is submitted herewith. In a telephone conference with Margo Furman on December 11, 2003, regarding the status of the second declaration, the Examiner stated that she was aware that a signed declaration had been submitted and had noticed the signed copy of this declaration which was also submitted in a reply in a related case (U.S.S.N. 09/822,682) on September 5, 2003.

Accordingly, because the Examiner did not properly consider the Second Declaration submitted with the last reply, Applicants respectfully request that the Examiner withdraw the

finality of the office action, and enter and properly consider the second Declaration and the arguments presented regarding the Declaration in this and in the previous response filed on July 30, 2003.

Rejections Under 35 U.S.C. § 112, first paragraph

Enablement

Claims 1, 6, 14-18, 20-23, 53-61, 63-67, and 75-122 are rejected as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1, 6, 14-18, 20-23, 53-61, 63-67, and 75-86 are canceled. The basis for the rejection is respectfully traversed.

1. Treatment of cancer is predictable within the context of the claimed methods

The Examiner argues as follows:

> [Applicants' previous arguments] have been fully considered but found unpersuasive because the claims are drawn to cancer treatment, not just making a collection of mutants and fragments, which can be done without undue experimentation in the current state of art. As presented in the previous Office Action, the cancer treatment is unpredictable. (Office Action, page 3.)

This rejection is respectfully traversed. Applicants have shown that the recited fragments' ability to inhibit endothelial cell migration *in vitro* correlates with the ability to treat an angiogenesis-dependent tumor *in vivo* (the Examiner is again urged to consider the previous arguments and declarations that have not yet been properly considered on this point). In addition, Applicants have provided *in vivo* data showing that fragments of TSP-2 that fall within the claims work to inhibit tumor growth. For example, Applicants have shown that the procollagen domain of TSP-2 inhibits tumor growth *in vivo*. See, e.g., Figure 3 of the first Declaration of Michael Detmar ("the First Declaration"), filed with the response of October 1, 2002, which shows that growth of A431 tumors in mice injected with the procollagen domain (PC) was reduced relative to growth of tumors in mice injected with PBS. See also Figure 4 of

the First Declaration, which also shows that tumors growing in mice injected with 1 mg/kg of the procollagen domain of TSP-2 had a smaller volume than tumors in control mice. Thus, the fragment of TSP-2 used in these experiments, which falls within the claims, is functional as claimed.

The Examiner provides additional arguments as follows:

> Applicant's argument using the cancer treatment data presented in the First Declaration using about [sic] a 600-aa N-terminal specific fragment of TSP-2 is not commensurate in scope [sic] of the claims because the claims are not limited to method [sic] of treating skin cancer or squamous cell carcinoma (A431 cell lines) shown in the declaration using the specific fragment...The specification...does not teach the specific fragment being used in the first Declaration.

Here, it is alleged that the claims are not enabled because data presented in the First Declaration employs an animal model using squamous cell carcinoma tumor lines, and Applicants have not shown that the methods work for every cancer. This grounds for rejection is traversed. The claims are limited to treatment of subjects with angiogenesis-dependent tumors. As noted on page 17, line 5 of the response filed on July 30, 2003, the A431 *in vivo* tumor model used in the specification and discussed in the First Declaration is an art-recognized tumor model. If one performs a search for the phrase "A431 tumor cells" in the PubMed database (http://www.ncbi.nlm.nih.gov/entrez/query), over 1380 references are revealed, many of which are concerned with evaluating efficacy of anti-tumor agents using the A431 cell/murine *in vivo* model. This model is recognized as correlating with angiogenesis-dependent (solid) tumor growth. Therefore, the efficacy of the claimed methods in this model correlate with treatment of angiogenesis-dependent tumors. Furthermore, the specification also contains data illustrating efficacy of TSP-2 in inhibiting growth of a second model cell line, malignant melanoma MeWo cells.

Moreover, the Examiner is asked to consider the remarks in the Second Declaration, in which Dr. Michael Detmar states that "the work described in the specification (and additional work described in my previous declaration dated September 27, 2002), demonstrates that TSP-2 and TSP-2 fragments can inhibit microvascular endothelial cell migration *in vitro* and confirms

that TSP-2 and TSP-2 fragments can treat angiogenesis-dependent tumors *in vivo*." (Second Declaration, page 2, paragraph 4; emphasis added). He further states that "one of ordinary skill in this field would understand that inhibiting any one of the steps necessary for angiogenesis to proceed normally would inhibit growth of any angiogenesis-dependent tumor. Thus, the ordinary skilled artisan would understand that the claimed methods can be useful in treating any tumor dependent on angiogenesis." (page 2, paragraph 6; emphasis added). The Examiner has not considered this evidence and is respectfully requested to do so.

The Examiner also argues that "the transfection data in the specification is not commensurate in scope [sic] of the claims because instant claims require administering protein or peptide directly." This is traversed. The Examiner is asked to consider the nature of the data and the very detailed explanations provided in the reply mailed on July 30, 2003, which have apparently not been considered or even read. As noted in that reply, TSP-2 is a secreted protein. The activities of TSP-2 are due to the effects of TSP-2 protein acting ***in trans*** on cells, and thus do correlate with administration of protein. The TSP-2 produced by the cells does not directly reduce growth of the cells themselves, but rather, reduces angiogenesis of tumors formed by the cells. If the Examiner intends to maintain this ground for rejection, she is asked to explain why she believes that this data does not correlate with administration of protein, in view of these facts.

2. Making and using of functional TSP-2 fragments is enabled

The Examiner states:

> Although endothelial migration assay is well known in the art, the specification does not provide guidance about how to make and use "a fragment thereof capable of inhibiting endothelial cell migration, wherein the fragment comprises **at least 10 contiguous amino acids of either (a) a procollagen domain of TSP-2**" in a method of treating cancer. (Office Action, pages 3-4, emphasis original.)

In support of the rejection, the Examiner notes data in Figure 7 of the specification which indicates that certain fragments of TSP-2 derived from procollagen domains did not inhibit endothelial cell migration. The reasoning of this grounds for rejection is flawed. That some of

these fragments did not inhibit endothelial cell migration does not mean that the claims are not enabled. The question is not whether it is possible to make a fragment that does not work (as the Examiner seems to believe), but rather whether one of ordinary skill can produce, without undue experimentation, fragments that do work, in which the activity is not abolished. The demonstration that particular fragments did not inhibit endothelial cell migration in an assay merely indicates that the assay is useful for distinguishing functional from non-functional fragments, and therefore supports enablement.

The Examiner also implies that the claims are not enabled because they are not limited to use of the fragment described in the First Declaration, and that this fragment is not taught by the specification. This is traversed. The Examiner acknowledged that the specification supports a fragment comprising an amino acid sequence encoded by nucleotides 294-1883 of SEQ ID NO:1. The fragment is similar to the fragment used in the Examples in the First Declaration, which corresponds to a polypeptide encoded by nucleotides 213-1883 of SEQ ID NO:1. In the Office Action mailed January 30, 2003, the Examiner issued a new matter rejection over claims directed to methods of using TSP-2 fragments comprising amino acid sequences encoded by nucleotides 294-1883 of SEQ ID NO:1. This rejection was argued in the reply sent on July 30, 2003 and was overcome (see page 21 of the reply mailed July 30, 2003). The genus of fragments recited in the claims includes a polypeptide encoded by nucleotides 213-1883 of SEQ ID NO:1. The fact that the specification does not contain *in vivo* data which uses a fragment identical to the fragment in the First Declaration does not render the claimed methods non-enabled. As discussed in previous responses, the law does not require Applicants to describe every conceivable embodiment of the invention. Ample guidance is provided by the specification, and other embodiments can be determined without undue experimentation.

The Examiner notes several broad grounds for non-enablement where she states "considering unpredictability in the cancer treatment art, broad scope of claims, insufficient guidance with regard to various recited cancer treatments with various claimed products, it is maintained that undue experimentation would be required to practice the invention as claimed."

The Examiner is respectfully requested to read and consider the detailed arguments in rebuttal of these grounds for non-enablement presented in the last 3 replies and 2 declarations filed in the present application. In summary, the claims are narrow in that they recite fragments with specific structural and functional limitations that are easily assayable, and recite treatment of a particular class of tumors, i.e., angiogenesis-dependent tumors (as opposed to "all cancers"). Applicants have shown that the claimed methods inhibit angiogenesis and tumor growth *in vivo* using art recognized models of angiogenesis-dependent tumors. The skill in the art is high and the guidance in the specification is substantial. In view of the foregoing, Applicants request withdrawal of the rejection.

Written Description

Claims 1, 6, 14-18, 20-23, 53-61, 63-67, and 75, 76, 84-104, 106-112, and 118-121 are rejected as failing to comply with the written description requirement. The Examiner states that "the claims do not associate any function for 90% identical structure to SEQ ID NO:2."

This rejection is traversed. Claims 1, 6, 14-18, 20-23, 53-61, 63-67, and 75-86 are canceled. Applicants note that claims 87-122 are directed to methods of treating a subject with a polypeptide comprising the amino acid sequence of SEQ ID NO:2 or a fragment thereof. These claims lack the 90% identity limitation; therefore, this basis for the rejection does not apply to the pending claims.

The Examiner also states, "[t]he specification does not teach any structure of a fragment comprising at least 10 contiguous amino acids of a procollagen domain of TSP-2 capable of inhibiting endothelial cells." This grounds for rejection is traversed. The specification discloses the explicit location of the procollagen domain in the TSP-2 polypeptide, discloses fragments of at least 10 contiguous amino acids, discloses methods of making and testing such fragments for the ability to inhibit endothelial cell migration, and discloses that such fragments can be used to treat certain tumors. Given this disclosure, a skilled artisan would immediately understand that Applicants were in possession of the recited fragments for the recited use. Under the Examiner's

reasoning, a working example would be required to satisfy the written description requirement. That is not the law.

Moreover, Applicants note that, while the Examiner agrees that peptide 7 has the recited function, the Examiner still rejected claims directed to uses polypeptides containing peptide 7 for lack of written description. See, e.g., claim 88, which is directed to methods for treating subjects with polypeptides comprising the sequence of SEQ ID NO:10. SEQ ID NO:10 and peptide 7 are the same peptide.

In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

New Matter

The Examiner newly rejected claims 1, 6, 14-18, 20-23, 53-61, 63-67, and 75-122 as lacking support in the specification. The Examiner states that "although the specification at page 2, lines 15-20 has support for unwanted cell proliferation, unwanted angiogenesis, benign or malignant unwanted cell proliferation, it does not have support for the treatment of an angiogenesis-dependent tumor."

This is traversed. There is ample support for this phrase in the specification as filed. See, e.g., page 2, lines 15-17 where it states that "the present invention is based, in part, on the discovery that overexpression of TSP-2 decreases tumor size *in vivo*. The invention features methods to modulate unwanted angiogenesis and tumor growth." Clearly, the treatment of tumors and inhibition of angiogenesis were contemplated at the time the specification was filed. The knowledge that tumors rely on angiogenesis was known at the time. See, for example, the first sentence of the Background, where it states that "in order to grow beyond minimal size and to metastasize, tumors need to induce the growth of new blood vessels (angiogenesis) providing a lifeline for tumor sustenance and waste disposal." Treatment of tumors is directly disclosed in the specification. Angiogenesis-dependence of tumors is also directly disclosed in the specification. As the Examiner is aware, whether particular technological information is new matter depends on the facts of the case, the nature of the disclosure, the state of the art, and the nature of the new matter. The disclosure and the state of the art amply support the phrase

"angiogenesis-dependent tumors". Thus, treatment of angiogenesis-dependent tumors, while not disclosed *in haec verba*, does not constitute new matter. Applicants also note that the term "angiogenesis-dependent tumor" was suggested by Examiner Yu and Examiner Caputa in the interview of July 8, 2003 with the undersigned.

Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: May 19, 2004

Louis Myers, Reg. No. 50,635
Louis Myers
Reg. No. 35,965

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906